REMARKS

The specification has been amended in response to the Examiner's request. Applicants' undersigned representative apologizes for the inadvertent substitution of the word "label" for "reagent" and appreciates attention being called to this by the Office. This obvious (but undetected by the undersigned) error has been corrected.

The abstract and title have also been amended.

The claims have been amended for clarity. The asserted redundancy of "particulate" has been removed from claim 1 and the characteristics of the second signal generating moiety, it is believed, are more clearly defined. Applicants understand that the previous wording of the claim wherein the second signal generating moiety "of standardized intensity" was confusing and obscured the nature of the invention. This has been amended to read "a second signal generating moiety which emits the same wavelength at the same intensity from all different labels." This defines the "clamped value" associated with the various labels. It is believed that this further obviates the assertion that there is no antecedent support in the specification, as further articulated below.

Minor editorial amendments have been made to claims 2 and 3; "the" has been changed to "a" before "detection space" to moot the issue of lack of antecedent basis. "Detection space" is defined on page 3 of the specification in paragraph 13 as "the area or volume represented by a signal which is detected, typically by means of microscopy techniques, such as confocal microscopy or wide-field microscopy." As pointed out in that paragraph, the detection space cannot be smaller than the wavelength of light used for detection.

Claim 4 has been amended to correct a typographical error. Claims 5 and 6 have been amended for clarity and to make them less verbose.

New claim 7 is supported on page 4, paragraph 16, new claim 8 on page 3, paragraph 13, and new claim 9 is supported by the explanation in paragraphs 22 and 23.

No new matter has been added and entry of the amendment is respectfully requested.

The Invention

The invention permits the practitioner to ascertain the number of particles that are responsible for a signal generated in a single unit of an environment called a "detection space." The dimensions of the detection space are determined by the resolving power of the observation, but in no event can the detection space be smaller in size than the wavelength of the signals being measured. Because very small particulate labels are often desirable, more than one particulate label may be present to generate a signal from a defined detection space. For example, labels contained on particulate supports of 100 nm are often desirable; visible light is in a wavelength range considerably longer – about 450-700 nm. Because the interpretation of the signal can depend on the number of particles that are actually generating it (see, for example, page 2, paragraph 6 of the specification), it is important that the practitioner be able to determine the number of particles whose characteristic signals are being observed. The invention permits this counting of particles to be done.

Each label in a multiplexing composition contains a reagent which will bind it to a target and a means for generating a hue that will be characteristic of the particle bearing a particular reagent. The generation of this hue may be a result of a single signal generating moiety, but more commonly by a combination of two or more such moieties whose ratio determines the hue characteristic of the particular label coupled to a particular reagent. Because, as explained in the specification, when the hue results from these combination ratios, ambiguous results may be obtained, it is necessary to determine the number of particles responsible for the hue generated in the detection space.

This is accomplished by providing each of the particulate labels in the multiplexed composition with a second signal generating moiety that is uniform in all the particles and which generates a signal with a wavelength different from any of the hues that characterize the various particles. The intensity of emission of this commonly coupled second signal generating moiety provides this information since the intensity generated by a single particle is known and is the same for all particles in the composition. Thus, two particles will generate a signal at this second wavelength twice as intense as a single particle. It is this second signal that has a "clamped value."

Formal Matters

In response to the request made by the Office, the title of the invention has been changed, the abstract has been modified further to describe the invention (although it is difficult to do this in 25 words or less) and the mistake in terminology in paragraph 18 has been corrected.

The rejections under paragraph 2 of 35 U.S.C. § 112 have also been addressed by amendment. The redundancy of "particulate" has been removed, "standardized intensity" no longer appears and claims 2-3 and 5-6 have been amended in response to the criticisms made by the Office.

Respectfully, applicants believe that the recitation that the particulate support is coupled to at least two different signal generating moieties is fully supported by the specification. The rationale behind the contrary assertion is not entirely clear to applicants; it may have resulted from the asserted ambiguity of "standardized intensity." The description of the signal generating functions associated with the particles appears in paragraph 9 and is illustrated in paragraphs 22 and 23. It is believed that in view of the clarifying amendment to claim 1 and the discussion at the interview, this basis for rejection is overcome.

The Art Rejections

Claims 1-4 were rejected as assertedly anticipated by Han, *et al.,* and claims 5 and 6 as obvious thereover in view of Kauvar. Neither of these rejections is believed correct since Han does not describe the compositions or methods of the independent claims. Applicants appreciate that in view of the discussion at the interview, agreement was reached that Han does not teach the limitations of claim 1. Neither does Han in any way suggest these limitations. As that is the case, the outstanding rejections over Han, either alone or in combination are believed overcome. However, the following explanation is retained for purposes of completeness of the record.

A review of Han indicates that the particles described contain only the one or more first signal generating moieties required by claim 1 and do not contain the second signal generating moiety that emits the same wavelength at the same intensity from all of the different labels in the composition. As noted by the Office, Figures 1A and 1B of Han show the generation of various hues by altering the ratio of plurality of signal generating moieties, each hue being characteristic of an individual particle. There is no teaching in Han of a second signal generating moiety which emits a different wavelength from the hue generated by the one or more first signal generating moieties which wavelength is the same for all particles in the composition and which emits at an intensity which is the same for all particles in the composition. It is the presence of this second signal generating moiety that constitutes the invention. Applicants are unable to find a statement said to be set forth on page 633, column 2, lines 11-14, that all the particulate supports generate the same signal from the standardized signal generating moiety. Applicants do not find any description of a standardized signal generating moiety (*i.e.*, "clamped value") at all in Han.

Accordingly, the art rejections may be withdrawn.

It should not be necessary to discuss specifically the combination of Han with Kauvar since the combination, even when made, does not suggest the invention as claimed.

Chandler

Also discussed at the interview was a portion of Chandler, *et al.*, U.S. 5,981,180 where particles with particular hues (indeed hues generated by a multiplicity of fluorophores) were provided a moiety which had a signal that varied according to the reactivity of the particles with some other substance. Chandler concerns flow cytometric techniques and is not concerned with counting particles in a detection space that is larger than the size of the particles. The additional moiety in Chandler does not generate the same wavelength and same intensity of emission in all the particles of the multiplicity; emission varies even with respect to a single particle (due to its binding status). Thus, the particles discussed on the basis of Chandler at the interview do not suggest the invention either. Should a formal rejection be made over Chandler, more extensive argument will be supplied; however, applicants believe this was disposed of at the interview.

CONCLUSION

The specification and claims have been amended to clarify further the subject matter of the invention. Applicants appreciate the agreement at the interview that the clarifying amendments demonstrate that the quantum dot-tagged microbeads of Han lack an essential feature of the invention, and thus do not anticipate the claims and do not render any claims obvious. Accordingly, applicants respectfully request that claims 1-9 be passed to issue.

Should formal matters remain that might be resolved over the telephone, a call to the undersigned at the number below would be appreciated.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 388512010900.

Respectfully submitted,

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